REMARKS

Claims 1-25, 52-58, and 62-86 are pending. No amendments to the claims are presented with this reply.

Rejections under 35 U.S.C. § 103(a)

Duck in view of Koster

Claims 1-7, 11, and 15-16 have been rejected as being obvious under 35 U.S.C. § 103(a) over U.S. Patent No. 4,876,187 to Duck et al. ("Duck") in view of U.S. Patent No. 6,043,031 to Koster et al ("Koster"). See the Office Action at 3-6. Claims 2-13 depend from claim 1. Applicants respectfully disagree.

Claim 1 relates to a probe array including an array surface, a first cleavage product of a first probe molecule which includes a label, and a second cleavage product of the first probe molecule which is immobilized at a first defined site on the array surface. The first cleavage product is bound to a first region of a target molecule, and the first cleavage product of the first probe molecule is noncovalently immobilized with respect to the array surface. The second cleavage product is bound to a second region of the target molecule. The array also includes a cleavage product of a second probe molecule immobilized on the array surface at a second defined site, wherein the cleavage product of the second probe molecule is not bound to a target molecule. The cleavage products of the first and second probe molecules are in contact with a cleaving solution. See independent claim 1.

Duck does not disclose a probe array. A probe array includes molecular probes on a surface, the position of each probe being determined separately. The array elements--areas on the surface having uniform composition of probes--taken together make up the array. Duck refers to a solid support but makes no mention of the support having different areas to which different probes are immobilized. And as the Examiner notes, Duck fails to teach two different probes on the array surface (Office Action at 3). Nor does Duck provide any teaching, suggestion, or motivation to arrange probes on different locations of a common surface, or of how to do so.

Duck's preferred solid supports, i.e., cellulosic material, controlled pore glass (CPG), and silicaceous material such as silica gel, are incompatible with successful multiplex detection of hybridization on a two-dimensional probe array. Such multiplex detection requires that immobilized probe molecules remain in spatially distinct spots, so that the identity of probes (and targets) can be determined from location. In other words, lateral diffusion of immobilized probes between different array locations must be very limited or absent entirely. Cellulose beads and CPG both have very high surface areas per particle, permitting lateral diffusion in the surface. Attempts to use such materials as a support for a two dimensional array will be frustrated by indistinct spots arising from lateral diffustion. In the context of Duck, these solid support materials are to be understood as being spherical or bead-like. See, for example, Fig. 1, and the methods describing "separately recovering the immobilized molecule," i.e., collecting the beads by centrifugation. Duck at column 7, lines 16-30 and column 8, lines 32-47. This procedure is impractical at best in the use of two-dimensional probe arrays.

Furthermore, at column 9, lines 20-42, Duck explains the desirability of high effective concentrations of probe molecules, indicating that relatively large quantities of probe molecules are required. The specification, at 89-90, indicates that a probe array element of typical size, saturated with immobilized probe molecules, includes just 10^9 molecules.

Koster is primarily concerned with mass spectrometric detection and characterization of nucleic acids. See, e.g., Title, Abstract, Summary ("[t]he instant invention provides mass spectrometric processes for detecting a particular nucleic acid sequence in a biological sample," col. 3, lines 47-49) and the examples appearing at columns 19-40. Figs. 1-19, 22-23, 25, 30-33, 35, and 38-45 depict schematic or experimental mass spectra.

Ultimately there is no motivation to combine Duck with Koster. Duck's methods and reasons for immobilizing probe molecules are inappropriate for two-dimensional, position-specific probe arrays. Koster does not make use of cleavage products and strongly prefers mass spectrometric detection. The objectives of the two references are divergent, as the means described to achieve those differing objectives.

Because a motivation to combine Duck with Koster is lacking, Applicants respectfully ask that this rejection be reconsidered and withdrawn.

Duck in view of Koster and additional references

Claims 8-14, 17-25 and 52-58 have been rejected as being obvious over Duck in view of Koster in view of various additional references. These rejections are briefly summarized below.

Claims	Rejected over Duck, Koster and -
8-13, 52-58	U.S. Patent No. 5,830,655 to Monforte et al. ("Monforte '655")
14	U.S. Patent No. 5,518,900 to Nikiforov et al. ("Nikiforov")
17-18, 22-25	U.S. Patent No. 6,040,138 to Lockhart et al. ("Lockhart")
19	U.S. Patent No. 4,874,492 to Mackay et al. ("Mackay")
20	Lockhart and U.S. Patent No. 5,770,360 to Kievits et al. ("Kievits")
21	Mackay and Kievits

As discussed above, claim 1 is nonobvious over the combination of Duck and Koster, there being no motivation to combine the two. None of the additional references remedy this defect. Nothing in these references teaches, suggests, or motivates a person of ordinary skill in the art to combine Duck's bead-based system with Koster's mass spectral detection array. Accordingly, claims 8-14, 17-25, and 52-58 are patentable over Duck in view of Koster and the additional references.

Monforte in view of Koster

Claims 62-74 and 76 have been rejected as being obvious over Monforte '655 in view of Koster. Office Action at 23-26 and 39-41. Applicants respectfully disagree.

Claim 62 relates to a probe array including an array surface, a first probe molecule immobilized on the array surface having a label and a selectively cleavable bond between the site of immobilization on the array surface and the label, where the first probe molecule is bound to a corresponding target molecule. A second probe molecule is also immobilized on the array

surface, and has a label and a selectively cleavable bond between the site of immobilization on the array surface and the label. The second probe molecule is not bound to a corresponding target molecule. The first and second probe molecules are in contact with a cleaving solution. See independent claim 62.

Monforte '655 does not teach two different probes on an array surface.[1] The Examiner argues that Koster supplies this missing element. Applicants have previously noted that Koster, while describing multiplexing, does not teach, suggest or provide motivation for an array having a cleavage product of a second probe molecule immobilized on the array surface. Koster simply does not describe the cleavage of an immobilized oligonucleotide strand. In response, the Examiner commented "[c]laim 62 merely requires probes having selectively cleavable bonds" and that "[b]ecause [Koster's] array has multiple different sequences, not all of the immobilized sequences would bind a single target. Thus, . . . at least one probe is bound to the target, at least a second probe is not bound to a target." Office Action at 40. The Examiner's reasoning implies that Koster teaches an array including at least one sequence for which no corresponding target molecule will be present in a sample applied to the array.

Applicants respectfully disagree that because Koster's array includes multiple different sequences, at least one probe necessarily remains unbound to a target. Koster's description of the sequence content of arrays is scant, and nowhere does Koster state or even hint that the array includes a probe that does not bind a target. A sample (i.e., a solution including a target molecule) need not include only a single target. Rather, it can include multiple target molecules, such that for each different probe in the array (i.e. for each array element), there is a corresponding target molecule. In such a case, Koster's array would lack second probe molecule is not bound to a corresponding target molecule. Indeed, where Koster illustrates an ordered array, each different array element is shown bound to a different target, and no element has unbound probe molecules. See, e.g., Figs. 3, 5, and 9. Nor does the text of Koster describe an array having a second probe molecule that is not bound to a corresponding target molecule.

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[1] To the extent that Monforte '655 suggests an array (e.g., at column 38, lines 42-55), cleavage is taught as a sequential operation. In other words, each array element is to be cleaved one at a time, so that the products released from the surface may be analyzed without interference from products derived from other array elements. In contrast, Applicants contemplate cleaving and analyzing all array elements simultaneously.

Because Koster fails to teach this limitation, the combination of Monforte and Koster cannot form the basis of a *prima facie* case of obviousness. The Applicants respectfully ask the Examiner to reconsider and withdraw this rejection.

Monforte '655 in view of Koster and additional references

Claims 75 and 77-86 have been rejected as being obvious over Monforte '655 in view of Koster in view of various additional references. These rejections are briefly summarized below.

Claims	Monforte '655, Koster, and -
75	Nikiforov
77	U.S. Patent No. 4,757,141 to Fung et al. ("Fung")
78-79, 83-86	Lockhart
80	Mackay
81	Lockhart and Kievits
82	Mackay and Kievits

As discussed above, claim 62 is nonobvious over the combination of Monforte '655 and Koster, as the combination of references fail to teach all of the claimed limitations. None of the additional references remedy this defect. Nothing in these references teaches, suggests, or motivates a person of ordinary skill to make an array having a second probe molecule that is not bound to a corresponding target molecule. Accordingly, claims 75 and 77-86 are patentable over Monforte '655 in view of Koster and the additional references.

CONCLUSION

Applicants ask that all claims be allowed. If the Examiner believes it to be helpful, the Examiner is invited to contact the undersigned representative by telephone at 202-429-3000. A petition for a one-month extension of time is enclosed with this reply. Please apply any charges or credits to deposit account 19-4293.

Respectfully submitted,

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